Misconduct in Research -Innocent Ignorance or Malicious Malfeasance?

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Misconduct in Research

- The Misconduct Scale
  - Innocent Ignorance
  - Surprising Sloppiness
  - Malicious Malfeasance
- Detecting, Correcting and Preventing Misconduct
- FDA Sanctions for Misconduct
- Resources

The Misconduct Scale

- **Innocent Ignorance**- misconduct of the uninformed kind
  - Noncompliance based on ***lack of understanding*** the regulatory consequences of an action. The act itself is usually intentional but the noncompliance is unintentional, not usually done to deliberately deceive

The Misconduct Scale

- **Innocent Ignorance**- misconduct of the uninformed kind
  - Backdating the subject's signature on a consent originally and the monitor is coming tomorrow!
  - Discarding source documents after accurate transcription and reporting transcribed data as original
  - Creating "source documents" from CRFs

The Misconduct Scale

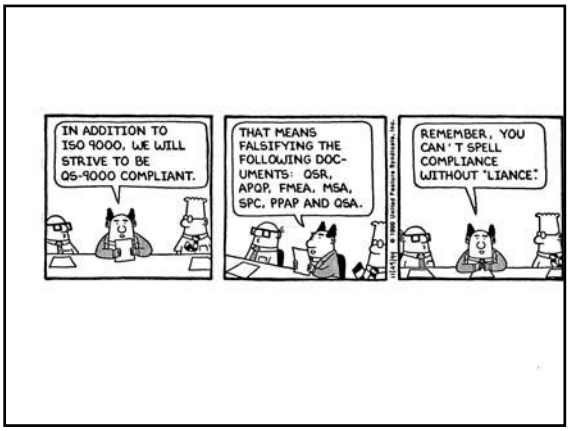
- **Surprising Sloppiness**- misconduct of the lazy kind
  - Noncompliance due to ***inaction***, inattention to detail, inadequate staff, lack of supervision. The act itself may be intentional or unintentional, the noncompliance is unintentional and usually repeated

The Misconduct Scale

- **Surprising Sloppiness**- misconduct of the lazy kind
  - Consent forms inadvertently not obtained from subjects
  - Blood pressures rounded to the nearest 5mm
  - Data estimated rather than actually measured
  - Data inaccurately transcribed or recorded
  - Protocol ignored or shortcuts taken

The Misconduct Scale

- **Malicious Malfeasance**- Misconduct of the sleazy kind
  - Usually noncompliance due to deliberate action to deceive or mislead includes The "F" Word: Falsification



What is Misconduct? FDA's Focus

- Deliberate or repeated noncompliance with the regulations can be considered misconduct, but is a secondary focus compared to ***falsification*** of data.
- Research misconduct does not include honest error or honest differences of opinion.

What is Misconduct? FDA's Focus

- **Recognizing Research Misconduct**
  - Research misconduct means ***Falsification of data*** in proposing, designing, performing, recording, supervising or reviewing research, or in reporting research results.

Falsification of Data

- **Falsification of data includes creating, altering, recording, or omitting data in such a way that the data do not represent what actually occurred.**

Falsification of Data

- Examples of falsification of data include but are not limited to:
  - creating data that were never obtained;
  - altering data that were obtained by substituting different data;
  - recording or obtaining data from a specimen, sample or test whose origin is not accurately described or in a way that does not accurately reflect the data
  - omitting data that were obtained and ordinarily would be recorded

Consequences of Falsification

- If falsification takes place in a clinical trial, it places all subjects in that trial at possible **safety risk**
- Falsification jeopardizes the **reliability** of submitted and/or published data and undermines the Agency's mission to protect and promote the public health

QA's Role in Dealing with Misconduct

- Prevention
  - Identify and eliminate/minimize risk factors for misconduct
- Detection
  - Monitor and recognize signs of fraud
- Correction
  - Promptly investigate and report fraud

Tips for Preventing Fraud

- Make sure all study staff have the necessary resources and support needed to accomplish their tasks
  - This includes training in what constitutes falsification
- Don't place needless requirements or unreasonable demands on the site
- Monitor sites closely and pay attention to complaints from site personnel
- Minimize the use of enrollment incentives

Detecting and Handling Scientific Misconduct

- **The Fiddes Case "lessons learned"**
  - What we observed,
  - What we didn't,
  - Why
- **How we can improve**
  - Tips for Detecting Serious misconduct
  - Systems for handling complaints of misconduct
  - Reporting misconduct to the FDA
  - Sharing information on Misconduct

New York Times May 17, 1999 RESEARCH FOR HIRE: SECOND OF TWO ARTICLES

A Doctor's Drug Studies Turn Into Fraud

By KURT EICHENWALD and GINA KOLATA

NY Time Allegations

100% source data verification = False sense of security

- Letter from one of the testing company's study monitors. "CONGRATULATIONS on meeting your enrollment deadline!" the monitor, (***YOUR NAME HERE***), wrote in a letter dated Feb.. "*I performed a 100 percent source document verification,(x-rays) and found no outstanding issues."*

Tip for ***Detecting*** Serious Misconduct

- **Get Technical**- Read and evaluate X-rays, EKGs, lab results, don't just inventory the source document

NY Times Allegation

The Slight of Hand Maneuver

- When a monitor hired by (***YOUR COMPANY NAME HERE***) asked to see the patient's medical chart, a study staff member quickly fetched the patient's medical chart, and pulled out every page that made reference to the disqualifying lung disease. Then, according to investigative documents, she turned the remaining records over to the monitor. The violation went undetected.

Tip for ***Detecting*** Serious Misconduct

- **Fill in the Blanks**- Question missing dates, times, information, offer to retrieve records yourself. Keep pulling on loose ends and see what unravels.

NY Times Allegation

The Emperor has no clothes Syndrome

- "Even when his employees spelled out their suspicions (to monitors) about what was happening. It wasn't that he was particularly adept at dodging their questions; rather, they *seemed reluctant to challenge such a prominent figure* in the drug-testing business."

Tip for ***Detecting*** Serious Misconduct

- **Don't be intimidated**- Tell the emperor he has no clothes and see if he tries to cover up.

NY Times Allegation

Blame the Monitor Maneuver

- "Several former coordinators for Fiddes said they had reported his unethical conduct to an independent study monitor working with (***YOUR COMPANY NAME HERE***). The Study Monitor sharply challenged Fiddes and his staff in her reviews of their paperwork. Fiddes chafed at the challenges, feigning outrage."

NY Times Allegation
Blame The Monitor Maneuver

- "Our integrity and reputation for performing high-quality clinical trial work has been injured, and we are justifiably upset," Fiddes wrote in a July 1995 letter to the sponsor, complaining about the monitor's demand. He insisted the sponsor "have a new monitor assigned to our site immediately."

Tip for ***Detecting*** Serious Misconduct

- **Don't shoot the messenger**- Believe the monitor, put the burden of proof on the Clinical Investigator.

NY Times Allegation
The Nurse D.I.T. Maneuver
The last refuge of a scoundrel

- "Dr. Fiddes replied that they were going to blame the study nurse for all of the problems, and he was going to say he had no knowledge of what was going on."

Tip for ***Detecting*** Serious Misconduct

- **Be suspicious of blame shifting-** Tell the Clinical Investigator he/she is responsible for the conduct of the study and is accountable for the results.

NY Times Allegation

- **"Monitors for the *government and the industry* never noticed any problems with Fiddes' bogus paperwork, which they reviewed during routine audits."**

NY Times Article Allegation

- "Why was Fiddes able to fool the monitors so easily? Because the oversight system is mostly designed to catch errors, not fraud".

Tip for ***Detecting*** Serious Misconduct

- **Expect Fraud-** Start from the assumption the records are bogus and the study is a fraud, and work back. Verify then trust.

NY Times Allegation

Fabrication the undetectable crime?

- "Another study on an antibiotic required that patients have a certain type of bacteria growing in their ear. No problem for Fiddes. He bought the bacteria from a commercial supplier and shipped them to testing labs, saying they had come from his patients' ears."

NY Times Allegation

- The FDA investigators asked (Fiddes), what evidence of fraud is there in the records reviewed by monitors and the government? What could the watchdogs have seen that would have allowed them to detect his fraud?

NY Times Allegation

- ***"Nothing,*** Fiddes replied. Had it not been for a disgruntled former employee, he would have still been in business."

Tip for ***Detecting*** Serious Misconduct

- **Cultivate Whistle Blowers**- Establish rapport with study staff, be approachable and available, listen to grievances, observe working conditions.

Tips for ***Detecting*** Serious Misconduct

- **Get Technical-**Read x-rays, EKGs, lab results, don't just inventory
- **Fill in the Blanks**-Question missing dates, times, information,offer to retrieve records yourself
- **Don't be intimidated**-tell the emperor he has no clothes

Tips for ***Detecting*** Serious Misconduct

- **Don't shoot the messenger**-believe the monitor, put the burden of proof on the CI
- **Be suspicious of blame shifting-**tell CI he/she is totally responsible for the conduct of the study
- **Expect Fraud**-Start from the assumption the records are bogus and the study is a fraud, and work back

Tips for ***Detecting*** Serious Misconduct

- **Cultivate Whistleblowers**-establish rapport with study staff, be approachable and available, listen to grievances, observe working conditions

NY TIMES Allegations

- Avoiding Detection: The F.D.A. Ignores an Early Warning -The government had its *first solid lead* on what was happening in Fiddes' office fully *17 months before Ms. X exposed his crimes to an FDA auditor*. FDA Investigators wrote memos about Ms. X's allegations, and forwarded them from Los Angeles to (***MY COMPANY NAME HERE)*** of the FDA.

How we can improve

Tips for ***Dealing*** with Serious Misconduct

Be Prepared- have a system in place to capture, document and deal with complaints of misconduct in a timely fashion. Follow your SOPs!!!!

Complaint Handling System Points to Consider

- **Policy on Complaints of Misconduct**
- **Procedures for Complaint Handling**
  - **Receiving, reviewing, reporting and processing**
- **Procedures for Documenting**
  - **Complaint files, forms, etc.**

Complaint Handling System Points to Consider

- **Policy**
  - All complaints should be ***assumed*** to be credible unless demonstrated to the contrary after thorough evaluation and supervisory review
  - All decisions on the follow-up action required for a complaint should have documented supervisory review and approval

Complaint Handling System Points to Consider

- **Policy**
  - **All** complaints should be documented and evaluated for follow-up upon receipt
  - Complaints requiring action should be followed up ASAP

Complaint Handling System Points to Consider

- **Policy**
  - Identify complaints that will be followed-up on a high priority basis e.g.
    - **Reports of gross abuse of subjects' rights that result or have the potential to result in death or injury**
    - **Reports of fraud, falsification or other criminal activity**
  - Assign due date to ensure that complaints are evaluated and acted on immediately.

Complaint Handling System Points to Consider

- **Policy**
  - **The receipt, follow-up, and action on all complaints should be documented from cradle to grave so that all decisions and actions can be reconstructed from the complaint handling documentation**

Sanctions in Regulated Clinical Research

- Purpose of sanctions
- Focus of sanctions
- Types of sanctions applied
- Issues

Purpose of Sanctions

Objectives

To protect and promote the integrity and quality of the development and approval process and to ensure that the rights and welfare of research subjects are adequately safeguarded

Purpose of Sanctions

Methods

- Exclude data found to be of questionable quality and integrity
- Restrict or exclude participation of parties who have corrupted the process through misconduct or malfeasance
- Notify affected parties to implement corrective action

Focus of Sanctions

- Individuals, Companies and Institutions involved in FDA regulated research
  - Clinical Investigators
  - Sponsors, CROs, Monitors
  - Institutional Review Boards (IRBs)
- Applications and data submitted to FDA

Clinical Investigator Sanctions

- Warning Letters
- Formal Disqualification
- Clinical Hold
- Voluntary Agreements
  - Restriction
  - Disqualification/total restriction
- Debarment
- Prosecution

Warning Letters

- Advisory letter communicating need for correction of serious deviations
  - Publicly available
  - Only apply to studies under U.S. regulation
  - Further action is required to assess and ensure corrections
    - » Resources required by FDA (CI, Sponsor)

Formal Disqualification

- Ineligibility to receive investigational products as determined through regulatory hearing process
  - Repeated or deliberate failure to comply with regulations or submission of false information
- Does not affect ability to practice medicine
  - Licensing is state regulated

Notice of Initiation of Disqualification Proceeding and Opportunity to Explain

- NIDPOE Letter
  - Notice of matters complained of required under 312.70
    - When FDA has information indicating that an investigator has
      - repeatedly or deliberately failed to comply OR
      - has submitted false information to FDA or sponsor
  - Letters posted on the web
    - http://www.fda.gov/foi/nidpoe/default.html

Formal Disqualification

- NIDPOE letter issued
- Response
- Informal Conference
- Evaluation
- NOOH issued
- Response
- Separation of Powers
- Counsel assigned
- Review by Counsel
- Presiding officer assigned
- Formal Hearing
- Presiding officer's report
- Comment period
- Commissioner's decision

Formal Disqualification

- Notification (When)
  - Delayed until action concluded
    - » Typical case may take 2-4 years
    - » Official action on potentially flawed data not possible
    - » Current and potential sponsors not alerted
    - » Investigator can continue to conduct studies

Formal Disqualification

- Notification (Who)
  - List available on the Internet under FOI
    - » http://www.fda.gov/ora/compliance_ref/bimo/dis_res_assur.htm
  - Direct notification only to limited parties
    - » IRB (optional?)
  - No formal notification to foreign authorities
    - » No notification received from foreign authorities

Formal Disqualification Issues

- Streamlining
  - Due process concerns

    Pending completion of disqualification
    - » Should/could an investigator's eligibility to receive investigational products be suspended ?
    - » Should/could potentially flawed data be excluded ?
    - » Should/could sponsors be notified ?
  - Consent Agreements

Clinical Hold

- Aug. 27, 2002- FDA announces availability of Draft Guidance-

The Use of Clinical Holds Following Clinical Investigator Misconduct

http://www.fda.gov/oc/gcp/whatsnew.html

Comment period closed on Nov. 25, 2002

Clinical Hold

What is a Clinical Hold?

- **Order issued by FDA to the sponsor to**
  - **Delay a proposed clinical investigation**
  - **Suspend an ongoing investigation.**
    - **no new subjects may be recruited to the study**
    - **patients already in the study should be taken off therapy involving the investigational drug unless specifically permitted by FDA in the interest of patient safety.**

Clinical Hold Draft Guidance

What circumstances would cause FDA to consider a clinical hold for investigator misconduct?

Answer- If FDA finds that human subjects are or would be exposed to an ***unreasonable and significant risk*** of illness or injury

When might FDA consider imposing a clinical hold before an enforcement action?

- If FDA finds evidence of one or more of the following:
  - Failure to report serious or life threatening AEs
  - Serious protocol violations such as enrolling ineligible subjects due to criteria that put them at increased risk
  - Other important failure to follow the protocol

When might FDA consider imposing a clinical hold before an enforcement action?

- If FDA finds evidence of one or more of the following:
  - Repeated or deliberate failure to obtain ***adequate informed consent including***
    - **Falsification of consent forms**
    - **Repeated or deliberate failure to disclose serious risks during the consent process**

When might FDA consider imposing a clinical hold before an enforcement action?

- If FDA finds evidence of one or more of the following:
  - Falsification of study data
  - Failure to obtain IRB review and approval of significant protocol changes

When might FDA consider imposing a clinical hold after an enforcement action such as a NIDPOE letter?

- If FDA finds evidence of one or more of the following:
  - **Repeated or deliberate failure to obtain adequate informed consent including**
    - **Falsification of consent forms**
    - **Failure to disclose serious risks during the consent process**
    - **Failure to provide informed consent in a language understand able to the subject**

When might FDA consider imposing a clinical hold after an enforcement action such as a NIDPOE letter?

- If FDA finds evidence of one or more of the following:
  - Repeated or deliberate failure
    - **to limit administration of the test article to subjects under supervision of the CI**
    - **to comply with conditions placed on the study by the IRB, sponsor, or FDA;**

When might FDA consider imposing a clinical hold after an enforcement action such as a NIDPOE letter?

- If FDA finds evidence of one or more of the following:
  - **Repeated or deliberate failure**
    - **to obtain review of a study plan by an IRB**
    - **to follow the signed investigator statement or protocol, e.g., by enrolling subjects who should have been excluded because of concomitant illnesses that put those subjects at greater risk**

When might FDA consider imposing a clinical hold after an enforcement action such as a NIDPOE letter?

- If FDA finds evidence of one or more of the following:
  - **Repeated or deliberate failure**
    - **to maintain accurate study records or submit required adverse event reports to the sponsor**
    - **falsification or concealment of study records, e.g., by substituting in study records the results of biological samples from subjects who met the inclusion criteria for samples of subjects who did not meet the inclusion criteria, or by fabricating subjects**

Consent Agreements

- Voluntary agreement between the Center and clinical investigator
- Offered as an expedited alternative at the ***outset*** of the formal disqualification process
  - Disqualification by consent
  - Lesser restrictions
    - number of studies
    - oversight by another investigator
    - third party verification of data

Consent Agreements

- Advantage
  - Speed for all parties
    - Data can be excluded
    - All affected parties notified (by letter and list)
  - Ability to tailor terms
  - No formal determination of guilt

Restrictions

- FDA may allow clinical investigators to enter into restricted agreements when the agency believes that lesser sanctions than disqualification would be adequate to protect the public health.
  - Clinical investigators are ***still eligible to receive investigational products,*** provided they conduct regulated studies in accordance with the restrictions specified in their agreement with FDA and all applicable regulatory requirements.

Restriction

- "Totally Restricted" versus "Restricted"
  - **"Totally restricted"** investigators are ineligible to receive investigational products (absent reinstatement).
  - **"Restricted"** investigators are still eligible to receive investigational products, provided they conduct regulated studies in accordance with the restrictions specified in their agreement with FDA and all applicable regulatory requirements.

Sanctions for Sponsors*

- Resulting from problems
  - With submissions to FDA
  - At the clinical site

*CROs that assume sponsor responsibility by contract are liable to sponsor sanctions

Sanctions for Sponsors

- Problems with submissions
  - » Untrue statements of material fact
  - » Submitting a fraudulent application
  - » Pattern of errors or system-wide failure to insure integrity of submissions

Sanctions for Sponsors

- Submission based sanctions
  - – Application Integrity Policy
  - – Exclude data or delay approval
  - – Prosecution
    - » Criminal misconduct
  - – Debarment
    - » removes individuals from approval process
    - » FDA will not accept or review applications from debarred individuals or companies

Types of Sanctions

- Application Integrity Policy (AIP)
  - » Agency Policy
  - » Pattern or practice of wrongful acts
  - » Validity assessment required
  - » All applications whose integrity is in question
  - » Substantive scientific review is deferred
  - » Refusal to approve or withdrawal of approved applications

Types of Sanctions

- Exclude data or delay approval
  - AIP: multiple applications
  - Single applications

Debarment

- Debarment
  - Applies to an individual (or firm) convicted of a crime relating to drug development or approval process
  - Debarred person can't work in any capacity for a drug firm
  - FDA will not accept or review applications involving debarred persons or companies

Prosecution

- Prosecution
  - Individuals (or firms) can be criminally prosecuted under Title 18 of the U.S. Criminal Code for
    - » Fraud and False Statements
    - » Conspiracy
    - » Mail fraud

Sanctions for Sponsors

- Clinical Site
  - Problems
    - » Failing to properly monitor?
      - Vague and unenforceable regulations?
    - » Failure to promptly correct or terminate and report
      - Vague and unenforceable regulations?
      - Liability to sponsor for termination and reporting of Cis?
  - Sanctions
    - » Warning Letter
    - » Exclusion of data

Minimal and Vague Regulatory Requirements

- Monitoring
  - 312.50: Ensure proper monitoring of investigations
  - 312.56(a): Monitor the progress of all clinical investigations.
- Correction, Termination and Notification
  - 312.56 (b) Promptly either secure compliance or discontinue shipments of drug;

    ...end the investigator's participation;

    ...notify FDA investigator's participation is ended

Regulatory Actions (Clinical Investigations)

Year(s)	93-96	97	98	99	00	01	02
Warning Letters	22	0	7	8	5	7	3
Disqualifications	2	0	0	2	0	1	1
Consent Agreements	7	1	4	5	0	0	1
NIDPOEs*	n/a	n/a	5	3**	3	2	1

*Notice of Initiation of Disqualification Proceedings and Opportunity to Explain

**One resolved in favor of CI

Last Updated:

Inspection Outcomes (1964-2001)

- Disqualifications 100
  (via hearing process or consent agreements)
- Restrictions/Assurances 30
  (via consent agreements)
- Prosecutions/Convictions 20*

*Includes some CI's who signed consent agreements.

Issue

- Sponsor Notification to FDA
  - Problems
    - » Only required when a investigator is terminated
    - » Time frame for reporting not specified
    - » Problems in completed studies not covered
    - » No regulatory penalty for failing to report
    - » Real or perceived liability inhibits termination and reporting by sponsor

Resources

- Enforcement actions information available on OGCP website at
  - http://www.fda.gov/oc/gcp/clinenforce.html
    - » NIDPOE
    - » Warning letters
    - » NOOH
    - » Disqualified
    - » Restrictions

FDA Believes Sponsors should Promptly Report...

- Any information they have that any person involved in human subject trials committed research misconduct
- Whenever the sponsor discovers misconduct
- Not just for clinical investigators and not just when a clinical investigator is terminated

Correcting Misconduct

- Reporting Research Misconduct
  - Name of the person(s)
  - Contact information
  - Specific identity of the affected research
    - » IND/IDE #, protocol, study title, and study dates
  - As much information regarding the research misconduct as is available to the sponsor.

Where to Report Misconduct

Medical Devices

- Office of Compliance, Division of Bioresearch Monitoring, (HFZ-310), Center for Devices and Radiological Health, FDA, 2098 Gaither, Room 130, Rockville, Maryland 20850, (301) 594-4718, fax (301) 594-4731.

Where to Report Misconduct

Drugs

– **Division of Scientific Investigations (HFD-45), Office of Medical Policy, Center for Drug Evaluation and Research, FDA, 7520 Standish Place, Room 103, Rockville, Maryland 20855-2773, (301) 594-0020, fax (301) 594-1204.**

Where to Report Misconduct

Biological Products

- **Office of Compliance and Biologics Quality, Division of Inspections and Surveillance, Center for Biologics Evaluation and Research, (HFM-650), FDA, 1401 Rockville Pike, Room 400S, Rockville, Maryland 20852-1448, (301) 827-6221, fax (301) 443-6748.**

Misconduct Website

FDA Homepage

- *www.fda.gov/ora/compliance.ref/default.htm*
  - »FDA Debarment list
  - »Disqualified/Restricted/Assurances list
  - »PHS Administrative Actions List

How You Can help

FDA Wants You to Recognize and Report Research Misconduct

There are worse jobs than being a QA Auditor